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# Reactions of CF<sub>3</sub>-substituted boranes with α-diazocarbonyl compounds

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# ABSTRACT

Boranes substituted with a CF<sub>3</sub>-group can be generated from methyl boronic esters RB(OMe)<sub>2</sub> and Me<sub>3</sub>SiCF<sub>3</sub>/KF followed by treatment with Me<sub>3</sub>SiCI. These boranes are stable only in coordinating solvents, and due to the increased Lewis acidity of boron, react rapidly with  $\alpha$ -diazocarbonyl compounds to give the products of transfer of the organic group from boron. Alkyl, aryl, vinyl, and alkynyl boronic esters can be used in this reaction.

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The reaction of organoboranes with diazo compounds constitutes an attractive process for C–C bond formation. Though discovered more than forty years ago,<sup>1</sup> only in recent times has this transformation begun evolving into an efficient synthetic method.<sup>2,3</sup>

The reaction mechanism involves the equilibration of a borane with a diazo group to generate zwitterionic intermediate **A** which undergoes migration of a substituent from boron accompanied by the elimination of nitrogen (Scheme 1). The  $\alpha$ -boryl carbonyl compound then readily tautomerizes to a boron enol ether, and the latter is hydrolyzed on work-up to give the product.

The efficiency of this reaction depends strongly on the ease of formation of species A, and therefore, the Lewis acidity of boron is an important factor. Thus, the reaction works well with trialkyl boranes,<sup>1</sup> but only one group is used. The use of aryl-BBN has recently been reported for the transfer of an aryl group, but for some diazo compounds migration of a borabicyclononane ring was observed.<sup>3</sup> On the other hand, conventional boronic acids and their esters, in which two oxygen atoms decrease the boron Lewis acidity, typically do not couple with diazoesters. However, recently, an example involving the reaction of excess 4-methoxyphenylboronic acid at 110 °C with ethyl diazoacetate was described.<sup>2a</sup> In another report, more reactive boroxines taken in stoichiometric amount (3 equiv of organic group) were employed at elevated temperatures (60–100 °C). Furthermore, the latter process was applied only for aryl and vinyl boroxines.<sup>2b</sup> In earlier publications, aryl- and alkyldichloroboranes were exploited at low temperatures, but competing transfer of chlorine with the formation of chloroketones was observed.  $^{\rm 4}$ 

It is well known that the Lewis acidity of boron can be increased dramatically by the introduction of perfluorinated substituents, and pentafluorophenyl boranes have been employed extensively as Lewis acids.<sup>5</sup> We reasoned that a perfluoroalkyl group would exert an even stronger electron-depleting effect.<sup>6</sup> Herein we report on the generation of the CF<sub>3</sub>-substituted boranes<sup>7</sup> and their subsequent reactions with  $\alpha$ -diazocarbonyl compounds.

In order to introduce the trifluoromethyl group, methyl boronic ester **1a** was treated with Me<sub>3</sub>SiCF<sub>3</sub> and potassium fluoride in 1,2dimethoxyethane (DME) at room temperature<sup>8,9</sup> (Eq. 1). The corresponding borate **2a** was isolated and its structure verified by NMR spectroscopy and X-ray analysis (Fig. 1).<sup>10</sup> This salt was an air -stable solid, which was stored in a tightly closed flask at room temperature for several months without any noticeable changes, and it could be safely handled in air.

$$\begin{array}{c} \begin{array}{c} Me_{3}SIGF_{3}\left(1.25\text{ equiv}\right) \\ Ph-B \\ OMe \end{array} \xrightarrow{\begin{tabular}{l} Me_{3}SIGF_{3}\left(1.25\text{ equiv}\right) \\ Fh-B \\ OMe \end{array} \xrightarrow{\begin{tabular}{l} OMe \\ Ph-B \\ OMe \end{array} \xrightarrow{\begin{tabular}{l} OMe \\ Ph-B \\ OMe \end{array} \xrightarrow{\begin{tabular}{l} OMe \\ Ph-B \\ CF_{3} \\ K^{+} \end{array}} (1)$$

$$2a \xrightarrow[-Me_3SiCl]{Solvent} Ph-B-OMe \ CF_3 \ Solvent \ CF_3 \ Solvent} dec.$$
(2)

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When borate **2a** was treated with chlorotrimethylsilane in donating solvents such as acetonitrile, DME or THF, complex **3a** was formed, which could be identified in solution by <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, and <sup>11</sup>B NMR spectroscopy (Eq. 2). However, concentration of the solution under vacuum, which was expected to cause decomplexation of the solvent molecule, led to decomposition. A similar intractable mixture was observed on treatment of salt **2a** with Me<sub>3-</sub>SiCl in non-coordinating CDCl<sub>3</sub>. Decomposition of the three-coordi-







**Figure 1.** X-ray structure of salt **2a** (thermal ellipsoids at 50% probability, ORTEP drawing). The potassium cation is omitted for clarity.

#### Table 1

Reaction of borate 2a with EDA



Entry	Solvent	Temp.	Additive	Yield of <b>5a</b> (%)
1	MeCN	rt	_	а
2	DME	–25 °C→rt	_	a
3	DME	-60→-10 °C	_	a
4	DME	−20 °C→rt	_	a
5	Et <sub>2</sub> O	−20 °C→rt	_	a
6	THF	−20 °C→rt	MeOH	82 <sup>b</sup>
7	DME	–20 °C→rt	MeOH	93 <sup>c</sup>

<sup>a</sup> Complex mixture.

<sup>b</sup> NMR yield.

<sup>c</sup> Isolated yield.

nate borane may be associated with the facile generation of difluorocarbene.<sup>11</sup>

The solution of **3a** in donating solvents was treated with ethyl diazoacetate (EDA, 1.1 equiv) under various conditions (Table 1). The evolution of nitrogen gas was typically observed at temperatures between -20 and 0 °C, and the mixture was kept for an additional one hour at room temperature. Though the starting compounds were consumed, only complex mixtures were formed after aqueous work-up (entries 1–5). We surmised that the initially formed boron ketene acetal **4** containing both an electron-rich double bond and a Lewis acidic boron center could readily decompose. It was rewarding to find that simple addition of a stoichiometric amount of methanol (1.1 equiv) prior to the diazo ester afforded ethyl phenylacetate (5a) as the sole product (entry 7). It is believed that methanol rapidly protonates species 4 preventing its decomposition. The reaction of **2a** with Me<sub>3</sub>SiCl and EDA/MeOH proceeded well in 1.2-dimethoxyethane. the same solvent used for the formation of starting **2a**, hence isolation of the borate salt was not necessary.

It is worthy of note that of the two organic substituents on boron (Ph and  $CF_3$ ), only the phenyl group undergoes migration. This phenomenon is in accord with the previously reported decrease in the migratory aptitude of a fluorinated group from boron.<sup>12</sup>

Besides methyl boronic ester, other esters were subjected to trifluoromethylation followed by the reaction with EDA (Table 2). Trifluoromethylation of neopentyl glycol and pinacol esters was noticeably slower, and the decreased yields of **5a** were due to incomplete conversion during the formation of salt **2**. With catechol ester, again the trifluoromethylation step was problematic, affording a complex mixture. Reactions of the trifluoroborate salt, PhBF<sub>3</sub>K, which upon treatment with Me<sub>3</sub>SiCl generated difluorophenylborane,<sup>13</sup> gave under various conditions less than 10% of the product. Methyl boronic esters proved to be superior substrates, and they were used for further studies.

While methyl esters can be obtained from widely available boronic acids, we encountered a practical problem at this point. Since some methyl boronic esters are sensitive to chromatography and even to moisture present in the air, they have to be prepared on large scale and purified by distillation. Moreover, for some boro-

Table 2Variation of the boronic ester



*i*: Me<sub>3</sub>SiCF<sub>3</sub>, KF, DME, rt *ii*: Me<sub>3</sub>SiCl, EDA, MeOH, DME

Entry	Substrate	Time	Yield of <b>5a</b> (%) <sup>a</sup>
1	Ph-BO	18 h	60
2	Ph-BO	18 h	33
3	Ph-B	12 h	<10
4	PhBF <sub>3</sub> K <sup>b</sup>	-	<10

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude material.

<sup>b</sup> The trifluoroborate salt was used instead of salt **2**.

nic acids (e.g., 4-iodophenylboronic acid), Brown's procedure with methanol/hexane<sup>14</sup> was found to be inapplicable. We proposed another protocol for generation of the methyl esters. Thus, the esterification of phenylboronic acid with trimethyl orthoformate was effected in the presence of catalytic amounts of trifluoroacetic acid (10  $\mu$ L per 1 mmol of boronic acid). The esterification was complete within 15 min, and subsequent evaporation of volatile materials under vacuum gave the pure boronic ester in quantitative yield (Eq. 3). The methyl ester obtained was suitable for further transformations, and this procedure was interchangeable with that using presynthesized material.

$$\begin{array}{cccc} PhB(OH)_2 & \xrightarrow{l} & PhB(OMe)_2 & \xrightarrow{Ph} & Ph & CO_2Et \\ & \mathbf{1a} & \mathbf{5a} & 93\% \end{array} \tag{3}$$
$$i: CH(OMe)_3 (2.5 equiv), cat. CF_3CO_2H \end{array}$$

A variety of boronic esters **1** were employed in the coupling reaction with EDA under optimized conditions. After the trifluoromethylation in 1,2-dimethoxyethane, simple addition of chloro-trimethylsilane followed by methanol and EDA, and brief stirring at room temperature gave product **5** (Table 3).

Table 3Reactions of boronic esters 1



*i*: Me<sub>3</sub>SiCF<sub>3</sub> (1.25 equiv), KF (1.0 equiv), DME, rt, 18 h *ii*: Me<sub>3</sub>SiCl (1.0 equiv), -20  $\rightarrow$  -10 °C, 20 min *iii*: MeOH (1.1 equiv), EDA (1.1 equiv), -20  $\rightarrow$  0 °C, 1 h; rt 1 h

Substrates with the boron attached to sp <sup>3</sup> , sp <sup>2</sup> , or sp carbor
atoms reacted successfully with EDA. Importantly, alkyl boronates
gave good yields of products (entries 1-3). Of particular note is that
the reaction proceeded when using a boronic ester containing a ke
tone group (entry 6), which suggests that nucleophilic trifluorom-
ethylation at boron proceeds faster. <sup>15</sup> Vinyl boronates were also
coupled with EDA (entries 7 and 8), though in the case of boronate
1i, the desired product 5i was accompanied by a small amount o
by-product 5ii (entry 8, shown in parentheses). The latter sub-
stance may originate either during protonation of the intermediate
boron enol ether, or upon isomerization of the product on work-up
Bromo-substituted boronate 1h also underwent the reaction point-
ing to the stability of the intermediate borate salt.

When 3-bromopropylboronic ester (**1k**) was subjected to standard conditions, a complex mixture was formed containing 9% of MeO-substituted product **5k** along with another species bearing an unreacted CH<sub>2</sub>B fragment (Scheme 2). It seems likely that in this case, formation of borate salt **2k** was accompanied by intramolecular displacement of the bromine by the methoxy group at a rate comparable to the formation of **2k**, leading to borane **3k**.<sup>16</sup> With chlorinated derivative **1l** the expected product **5l** was produced in 43% yield; this reflects the poorer leaving group ability of chlorine compared to bromine.

Entry	Boronate		Product		Yield (%) <sup>a</sup>
1	Ph B(OMe) <sub>2</sub>	1b	Ph CO <sub>2</sub> Et	5b	79
2	PhB(OMe) <sub>2</sub>	1c	PhCO2Et	5c	70
3	B(OMe) <sub>2</sub>	1d	CO <sub>2</sub> Et	5d	80
4	I-B(OMe) <sub>2</sub>	1e <sup>b</sup>		5e	85
5	B(OMe) <sub>2</sub>	1f	CO <sub>2</sub> Et	5f	83
6	O S B(OMe) <sub>2</sub>	1g	O CO2Et	5g	63
7	Br B(OMe) <sub>2</sub>	1h <sup>b</sup>	Ph CO <sub>2</sub> Et	5h	75
	Ph B(OMe) <sub>2</sub>		PhCO2Et	5i	72
8	1i	1i		5ii	(12) <sup>c</sup>
9	PhB(OMe) <sub>2</sub>	1j	Ph-=CO_2Et	5j	73

<sup>&</sup>lt;sup>a</sup> Isolated yield.

<sup>b</sup> The boronic ester was obtained from boronic acid using trimethyl orthoformate.

<sup>&</sup>lt;sup>c</sup> Ethyl (2*E*)-3-phenylbut-2-enoate (**5ii**) was obtained as a by-product.



i: Me<sub>3</sub>SiCF<sub>3</sub>, KF; Me<sub>3</sub>SiCl; MeOH, EDA





#### Table 4

Reaction of borate salt **2a** with various diazocarbonyl compounds





<sup>a</sup> Isolated yield unless mentioned otherwise.

<sup>b</sup> (1-Adamantyl)chloromethyl ketone (**7aa**) was formed as a by-product.

<sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>d</sup> No methanol was added.

Variation of the diazocarbonyl partner in reactions with borate salt **2a** is presented in Table 4. In reactions of diazoketones under typical conditions, the formation of small amounts of  $\alpha$ -chloroketones occurred, which proved difficult to separate from the desired products (entry 1). Apparently, this by-product is produced upon protonation of diazoketones with methanol complexed with the CF<sub>3</sub>-substituted borane followed by a chloride anion attack. The formation of  $\alpha$ -chloroketones can be avoided by using a silyl triflate instead of chlorotrimethylsilane. Reaction with ethyl  $\alpha$ -diazopropionate (**6d**) gave a complex mixture. However, a reasonable yield of the product could be obtained by performing the reaction without methanol (entry 6). This observation may signify that in

this particular case the intermediate boron enol ether is sufficiently stable.

In summary, we have demonstrated that boranes possessing trifluoromethyl, methoxy and various organic groups can be readily generated starting from the methyl boronic esters and Me<sub>3</sub>SiCF<sub>3</sub>. These boranes are stable only in donating solvents, and due to the increased Lewis acidity of boron, react with  $\alpha$ -diazocarbonyl compounds under very mild conditions.<sup>17</sup>

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.141.

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- 10. The crystal of **2a** ( $C_9H_{11}BF_3KO_2$ ) was monoclinic at 120 K, space group P21/c, a = 13.289(3), b = 6.8369(14), c = 12.765(3),  $\hat{A}$ ,  $\beta = 102.833(4)^\circ$ , V = 1130.8(4),  $\hat{A}^3$ , Z = 4, M = 258.09,  $d_{calc} = 1.516$  g cm<sup>-3</sup>,  $\mu(MOK\alpha) = 0.490$  cm<sup>-1</sup>,  $f(0 \ 00) = 528$ . 10030 reflections were collected using a Smart 1000 diffractometer, 2470 reflections were unique.  $R_1 = 0.0604$  was calculated against  $F^2$  for 1629 reflections with  $I > 2\sigma(I)$ . Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 827611) and are available free of charge on application from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ca.uk).
- Such a decomposition pattern is typical for highly Lewis acidic CF<sub>3</sub>-substituted boranes. For a discussion, see Ref. 7b On the other hand, analogous dimethylamino boranes Alk-B(CF<sub>3</sub>)NMe<sub>2</sub> and (CF<sub>3</sub>)<sub>2</sub>NAlk<sub>2</sub> have been wellcharacterized in the individual state, see: (a) Brauer, D. J.; Bürger, H.; Dittmar, T.; Pawelke, G. J. Organomet. Chem. **1995**, 493, 167–173; (b) Bürger, H.; Grunwald, M.; Pawelke, G. J. Fluorine Chem. **1986**, 31, 89–98.
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- 15. In the crude sample no product arising from trifluoromethylation of the carbonyl group was detected.

- 16. The boronic ester 1k itself can interact with KF which complicates the reaction mixture. Indeed, stirring 1k with KF in 1,2-dimethoxyethane for 18 h gave a milky suspension; <sup>1</sup>H and <sup>19</sup>F NMR spectra showed the formation of several unidentified products.
- 17. General procedure for the trifluoromethylation of boronates and subsequent reaction with EDA. KF (58.1 mg, 1.0 mmol) and Me<sub>3</sub>SiCF<sub>3</sub> (148  $\mu$ L, 1.25 mmol) were added to a solution of boronate **1** (1.0 mmol) in 1,2-DME (1.5 mL), and the mixture stirred overnight at room temperature. The mixture was cooled to  $-20 \,^{\circ}$ C, TMSCI (128  $\mu$ L, 1.0 mmol) was added, and the temperature was allowed to warm to  $-10 \,^{\circ}$ C over 20 min. The mixture was again cooled to  $-20 \,^{\circ}$ C, MeOH (45  $\mu$ L, 1.1 mmol) and EDA (116  $\mu$ L, 1.1 mmol) were added, and the temperature was allowed to warm to  $0 \,^{\circ}$ C over 1 h. The cooling bath was removed, and the mixture was stirred for an additional 1 h at room temperature. For the work-up, H<sub>2</sub>O (5 mL) was added with stirring, and the organic phase was extracted with hexanes (3 × 3 mL). The combined organic extracts were filtered through Na<sub>2</sub>SO<sub>4</sub>, concentrated, and the residue flash chromatographed on silica gel.

General procedure for the synthesis of methyl boronic esters. TFA ( $10 \mu$ L) was added to a mixture of boronic acid (1.0 mmol) and trimethyl orthoformate ( $273 \mu$ L, 2.5 mmol) and the resulting mixture stirred vigorously at room temperature for 15 min. The volatile materials were evaporated under vacuum to give virtually pure methyl boronic esters, which could be used in trifluoromethylation reactions and reactions with EDA.

General procedure for the reactions of borate **2a** with diazo compounds **6**. TMSCI (140 µL, 1.1 mmol) or TMSOTF (200 µL, 1.1 mmol) was added to a solution of borate **2a** (284 mg, 1.1 mmol) in 1,2-DME (1.5 mL) at -20 °C, and the temperature was allowed to warm to -10 °C over 20 min. The mixture was again cooled to -20 °C, diazo compound **6** (1 mmol) and MeOH (49 µL, 1.2 mmol) were added [in the case of ethyl diazopropionate (**6d**) the reaction was carried out without MeOH], and the temperature was allowed to warm to 0 °C over 1 h. The cooling bath was removed, and the mixture stirred at room temperature for the time indicated in Table 4. The work-up was the same as that used in the procedure with EDA.